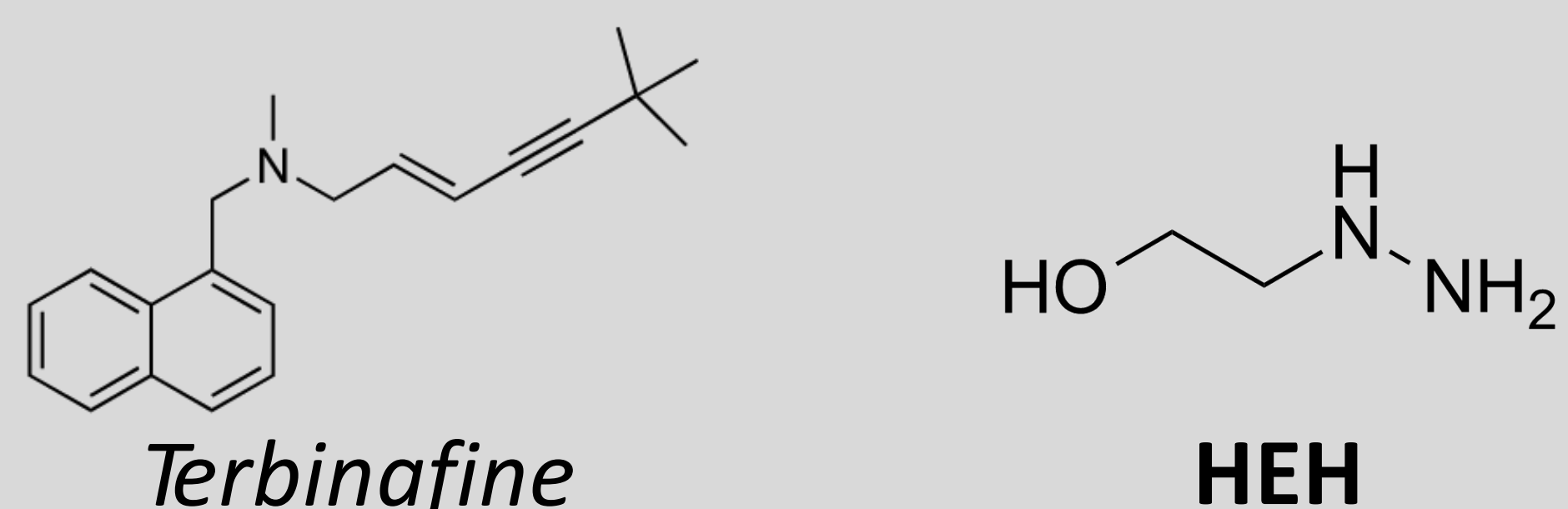
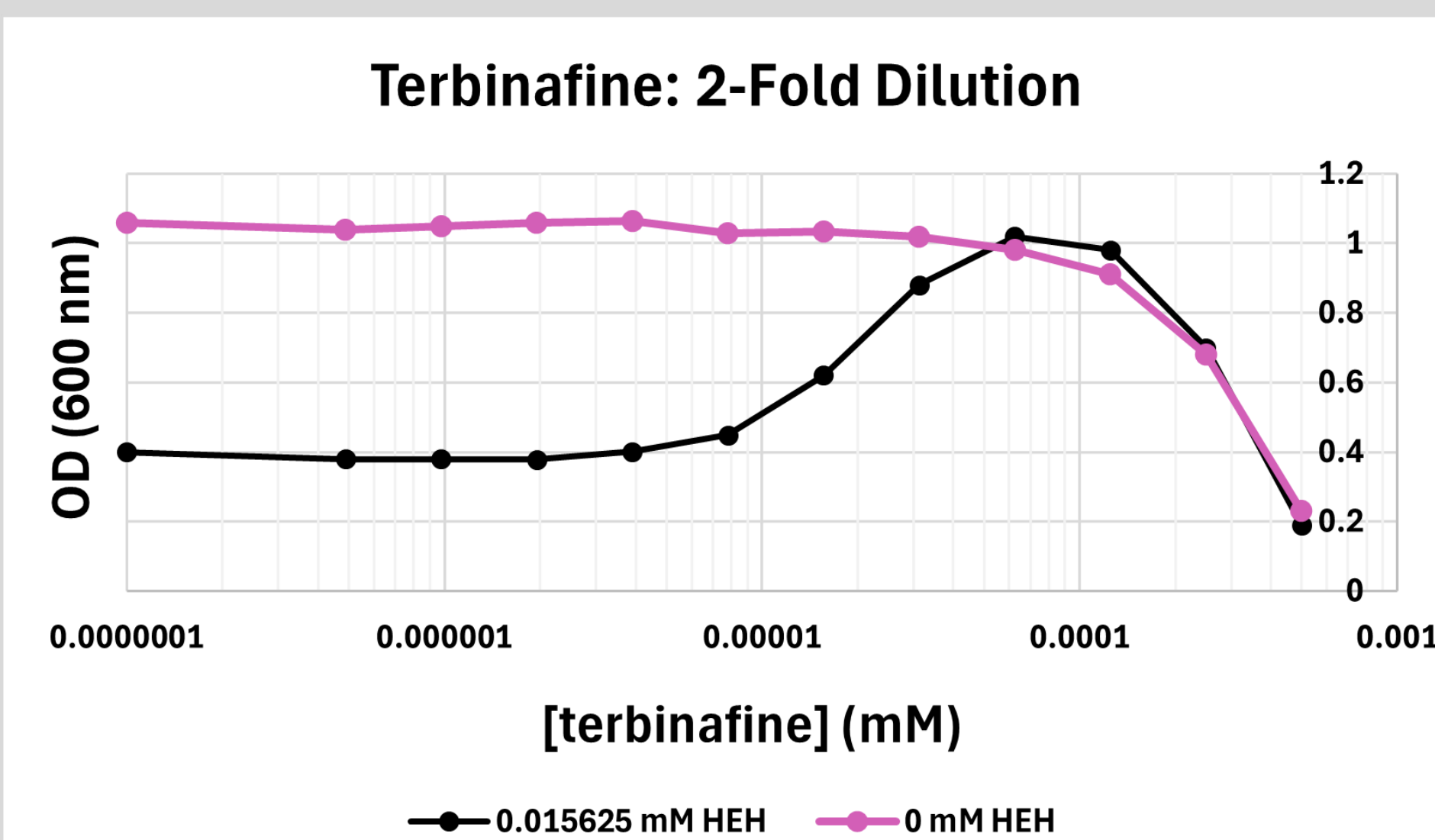


Background

- Antibiotic resistant microbes were responsible for an estimated 4.95 million deaths in 2019 [1]
- 2-Hydroxyethylhydrazine (**HEH**) is a novel antifungal which enters the cell via an amine selective transporting protein encoded by the gene **HNM1**
- **HEH** achieves significant growth inhibition at lower concentrations than many currently used antifungals
- Combinatorial treatments can increase the effectiveness of treatment while lowering toxicity [2]

Terbinafine and HEH

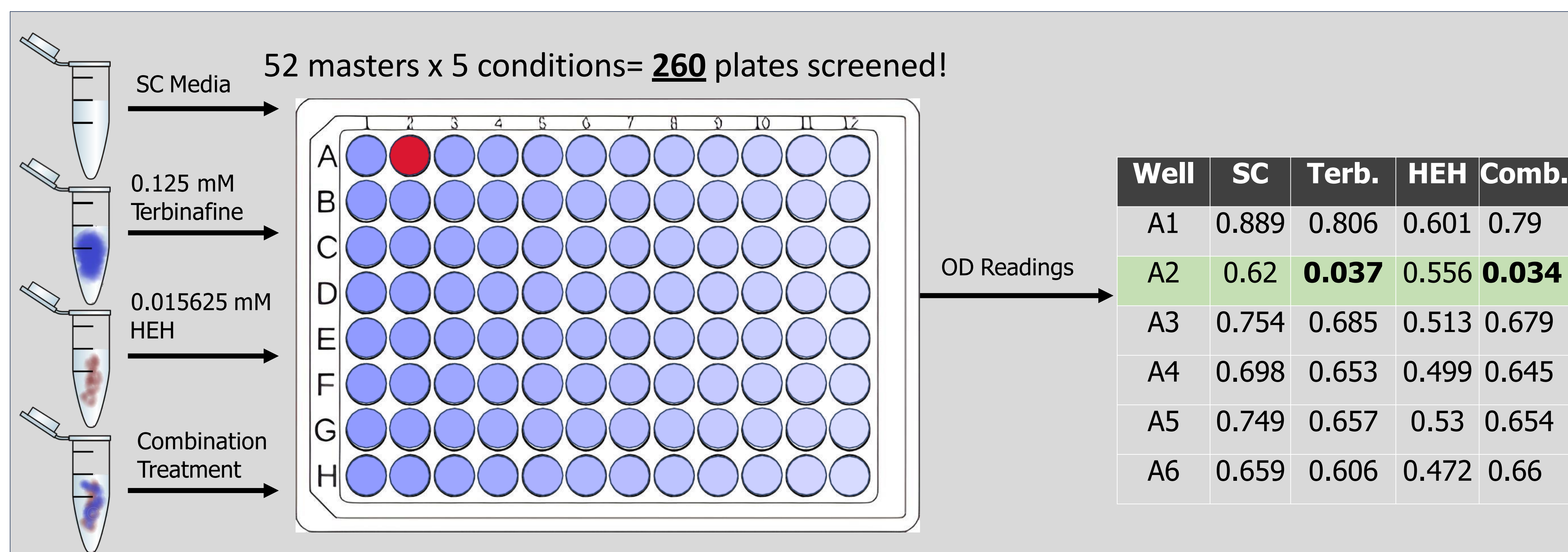
- When terbinafine and **HEH** are used in combination, a significant antagonistic relationship can be observed



Objective

- Determine the mechanism of antagonism between terbinafine and **HEH**

Methods: Nonessential Genetic Screening

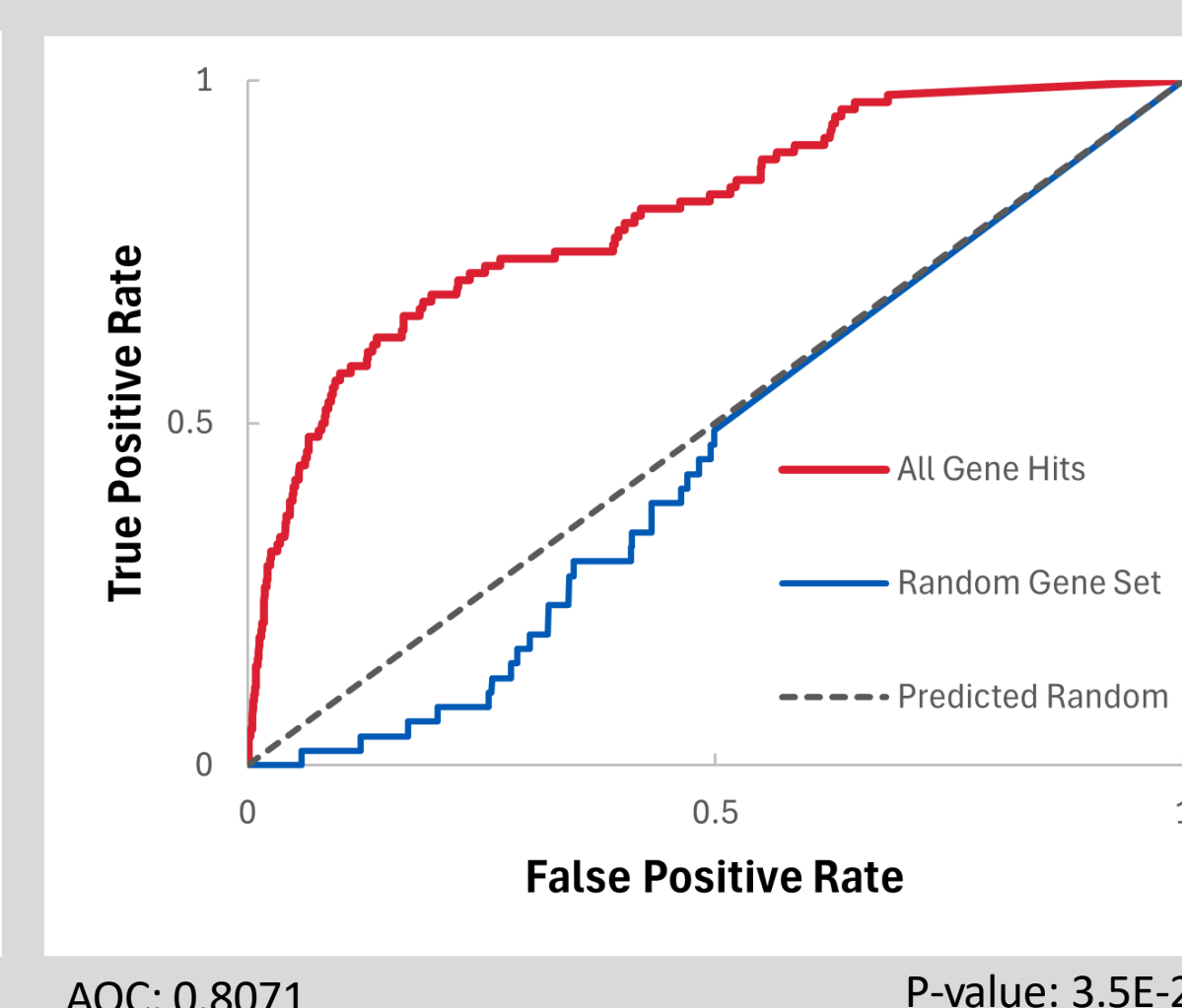


Results

All Mutant "Hits"

- The collected mutants were analyzed via a receiver operating characteristic curve, and gene ontology analysis
- Mutants were further categorized based on their sensitivity to **HEH**

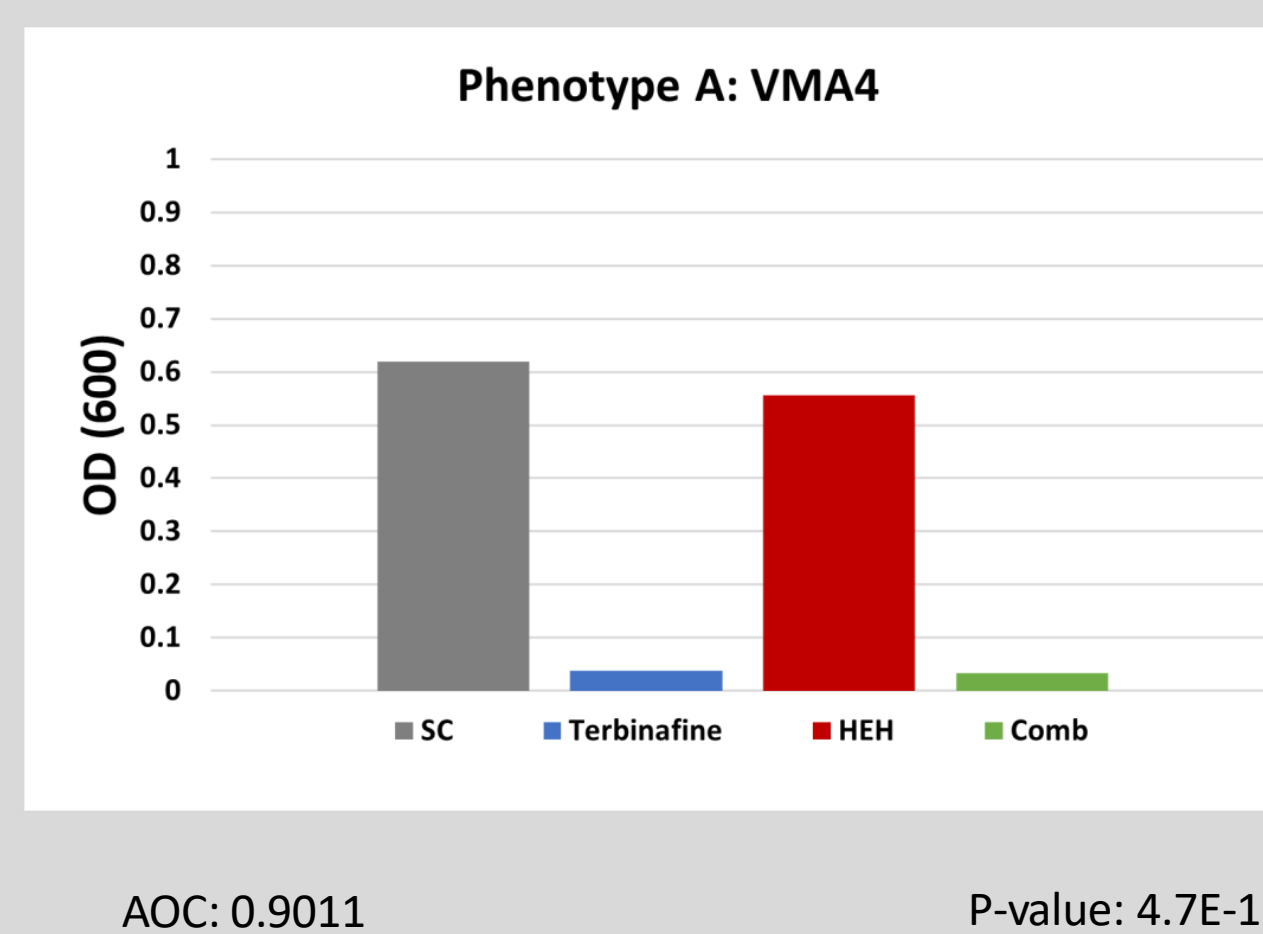
Gene Function	P-value	Examples of Affected Genes
Vacuolar Acidification	3.81E-10	VMA8, VPH2
Biological Regulation	6.42E-10	OPI1, VMA8, SIN4
Regulation of RNA	3.31E-08	OPI1, VPS15, PGD1
Biosynthesis Response to Stimulus	5.37E-07	OPI1, GAL11, MED2



Mutant "Hits": Phenotype A

- Mutants were not sensitive to **HEH**

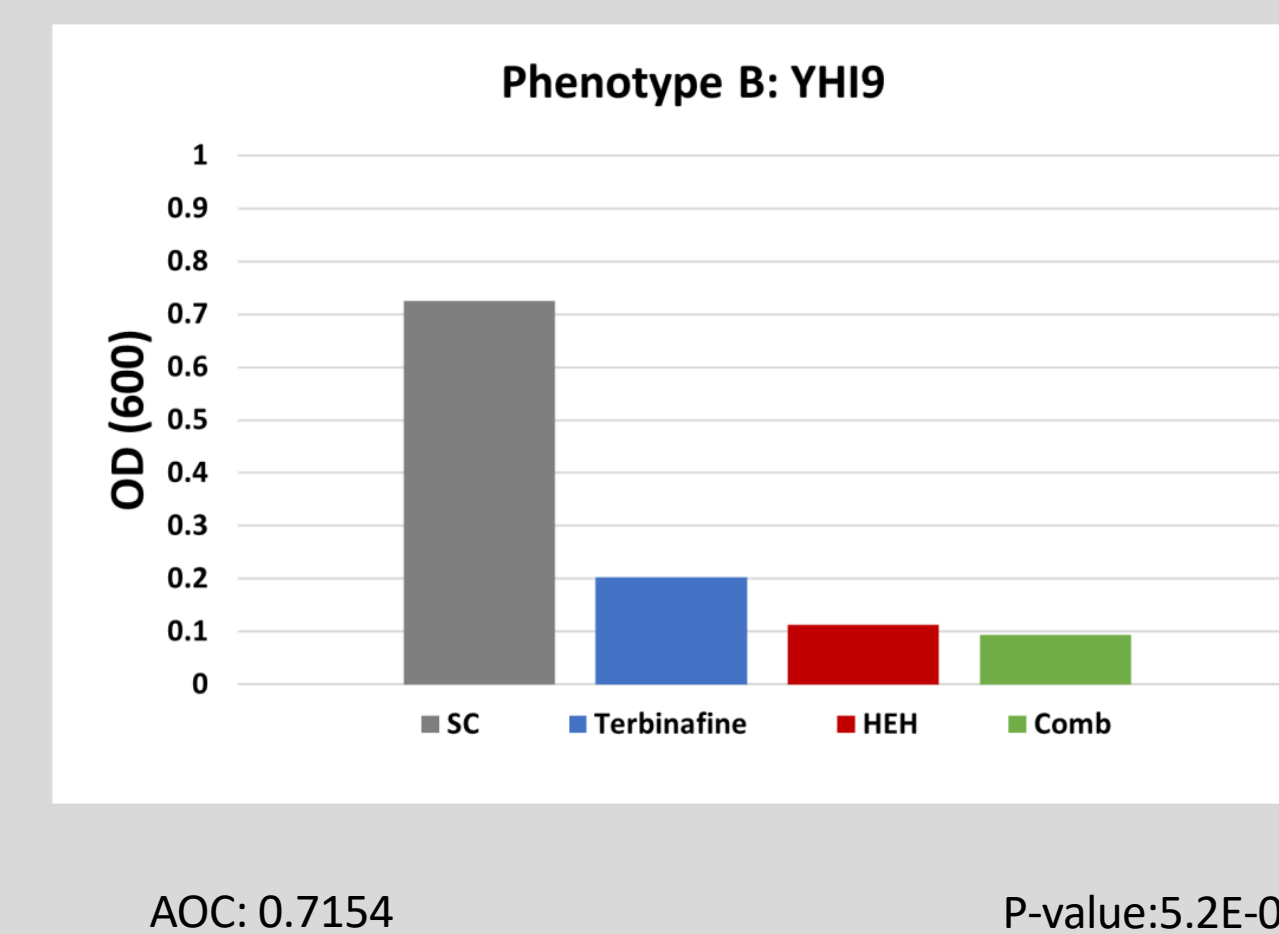
Gene Function	P-value
Vacuolar Acidification	6.93E-14
Biological Regulation	1.14E-07



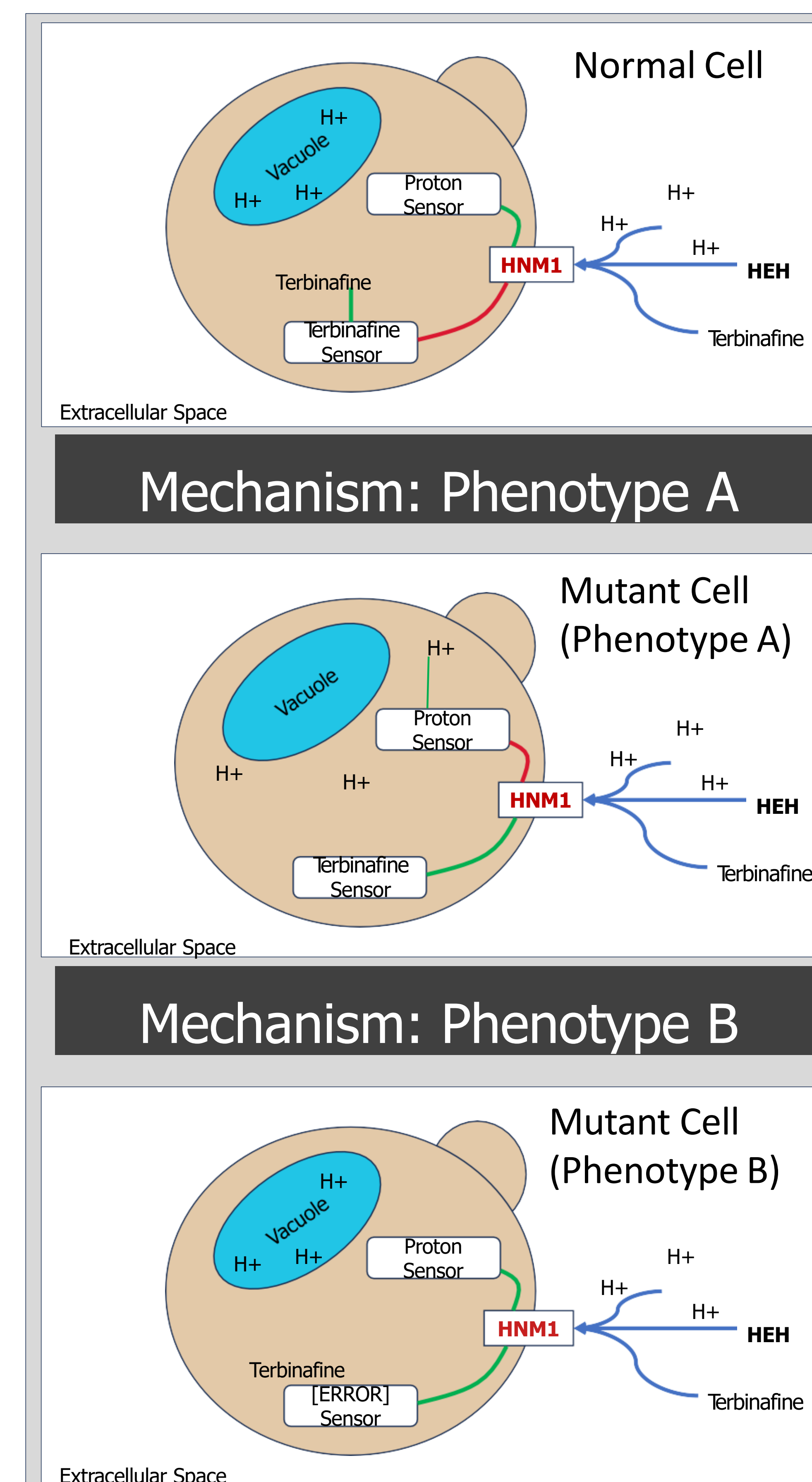
Mutant "Hits": Phenotype B

- Mutants were sensitive to **HEH**

Gene Function	P-value
Response to Stimulus	1.33E-05
Regulation of RNA Biosynthesis	2.48E-05



Proposed Mechanism



Future Directions

- Continue to investigate the link between terbinafine and **HNM1**
- Perform GC and TLC to analyze the lipid profile of yeast under our conditions

References:

1C. Murray, et al., "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis". Seattle, Washington, United States, The Lancet, Volume 399, Issue 10325, Pages 629-655, 2022. Accessed: June 17, 2024. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0140673621027240?via%3Dihub>

2R. Lewis, D. Kontoyiannis, "Rationale for combination antifungal therapy" Houston, Texas, United States, Pharmacotherapy, Volume 21, Issue 8P2, Page 149S-164S, 2012. Accessed: June 17, 2024. [Online]. Available: <https://pubmed.ncbi.nlm.nih.gov/11501988/>